CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
DICHLORPROP-P

Chemical Code #'s 2503, 5060, 5061 and 5336 Tolerance #'s 50305, 51432, and 52172
SB 950 # 069

Original: 8/17/00
Revised: 8/22/00

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	Data gap, inadequate study, no adverse effect indicated
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity (rat):	No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers through 164780 were examined. This includes all records indexed by DPR as of 6/6/00.

In the one-liners below:
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

File name: T000822, Revised by Peter Leung, 8/22/00

These pages contain summaries only. Individual worksheets may contain additional effects.

2,4 –DP = racemic mixture (cc no. 2503)
2,4-DP-p = Optically active isomer (cc no. 5060)
2,4-DP (Dichlorprop) (D-Form) = optically active isomer (cc no. 5060)
2,4-DP-p 2-EHE = ethyl hexyl ester (cc no. 5061)
2,4-DP-p DMAS = dimethylamine salt (cc no. 5336)

COMBINED, RAT

50305-008 034283 Mitsumori, K. (Study Director), "2,4-DP Acid (2-(2,4-dichlorophenoxy) propanoic acid): 24-month oral chronic dietary study in rats," The Institute of Environmental Toxicology (Tokyo), Sept. 1984. The original version reviewed by J. Christopher had no report number. A later duplicate report under Doc. No. 50305-027 gives "RZ-Report No.: 85/071." Report was re-examined by Aldous to provide tables for major findings. Eighty F344 rats/sex/group were dosed in diet with 0, 100, 300, 1000, or 3000 ppm 2,4-DP acid [racemic], 95% purity. Of these, 8/sex/group were sacrificed at weeks 26, 52, and 78 for hematology, clinical chemistry, urinalysis, and necropsies with histopathology. The balance were maintained for 2 years to evaluate lifetime chronic and oncogenicity parameters. NOEL = 100 ppm, based on reduced urinary specific gravity and reduced urinary protein content in males. Unbound (direct) bilirubin levels were also reduced at 300 to 3000 ppm in males, but there was little dose response, suggesting unlikely importance. Kidney-related findings, common at 1000 to 3000 in both sexes, included increased absolute and relative weights, grossly darkened color associated with increased brown pigment deposition in proximal tubular cells, and increased water consumption (females only), in addition to the low urine specific gravity and low urinary protein content. In addition to general exacerbation of the above findings at 3000 ppm, high dose findings included persistent body weight decrements, mild anemia (reduction of RBC count, HCT, and Hb), retinal atrophy/degeneration (females), liver enlargement and occasionally grossly darkened color, increased brown pigment deposition in hepatocytes (males), and a series of clinical chemistry changes commonly associated with liver and sometimes kidney function (increased alkaline phosphatase, AST, and ALT in males; increased albumin, decreased globulin, and decreased cholesterol in both sexes. Pigmentation in kidneys and liver stained as lipofuscin. Additional noted findings of unlikely toxicological importance included statistically significantly elevated prostatitis in 1000 to 3000 ppm males and non-significantly elevated osteosclerosis in 1000 to 3000 ppm females: neither of these indicated dose-responses. Study is **acceptable, with one significant deficiency: ophthalmology was not measured. It appears unlikely that this deviation from current guidelines influenced the outcome of the study. This failing was not cited by Dr. Christopher as a critical deficiency, and the re-review considers this insufficient reason to reverse the acceptable status of the study. Original review considered "possible adverse effects" due to changes in kidneys, liver, eyes, and bone. Since toxicologically important responses were limited to comparatively high dose levels, the re-examination recommends removing the "adverse effects" designation. Christopher 10/30/85, Aldous 6/1/00.

50305-009, -010, -011, -017 [Records 34284, 34285, 34286, 34287, 34288, and 34304]. Continuation of record 50305-008 034283, above: all associated with and reviewed with the original report.

50305-027 116329 Exact duplicate of record 34283 and associated records, above.

50305-002, 003, 004, 005, 006, 007. 34277, 34278, 34279, 34280, 34281, and 34282. "Oncogenicity Study in Rats with 2,4-DP", (CDC Research Laboratories, 4/18/85; in-Life study 1977-1979). 2,4-DP, purity not stated, was admixed with the feed at concentrations of 25, 50, or 200/(reduced to 150 mg/kg after 15 months) mg/kg/day and fed to 50 Sprague-Dawley rats/sex/group for 24 months. Adverse effects: hepatotoxicity, nephrotoxicity. Actual dose uncertain; incomplete (no diet analysis or statistics); **UNACCEPTABLE** (numerous protocol and performance deficiencies); Data are inadequate to assess toxicity. (J. Christopher, 10/28/85). NOTE: No oncogenicity was identified. Most kidney and liver toxicity was found at the highest dose level, which proved excessive, based on body weight and food consumption decrements. Nominal NOEL was apparently 25 mg/kg/day, based on some liver necrosis at the mid-dose. This study probably would not be classified as indicating a "possible adverse effect" by current review protocols. Comments by Aldous, 6/2/00 [no new worksheet].

CHRONIC TOXICITY, RAT

(See Combined, Rat, above)

CHRONIC TOXICITY, DOG

50305-031 158380 Bachman, S., K. Deckardt, C. Gembardt, and B. Hildebrand, "Dichlorprop-P - Chronic Oral Toxicity Study in Beagle Dogs - Administration in the Diet for 12 Months", Department of Toxicology, BASF Aktiengesellschaft, Ludwigshafen, FRG, Project # 33D0187/91167, 10/15/97. Five beagles/sex/group received Dichlorprop-P (91.9% purity) in the diet at 0, 120, 240, and 720 ppm for 12 months in a standard chronic study. Mean achieved dose levels were 3.5, 7.0, and 22.2 mg/kg/day in males and 3.9, 7.7, and 26.1 mg/kg/day in females. [A subchronic study performed at the same facility (50305-029 139379, described in the present review) found slight increases in blood clotting time and slight decreases in serum alkaline phosphatase at 175 ppm, whereas 525 ppm yielded additionally only slight reduction in RBC counts and increased diarrhea]. Chronic NOEL = 120 ppm (ulceration of gingiva in one male at 240 ppm). Major findings at 720 ppm were gingivitis and associated stomatitis, evidently specifically due to oral tissue response as the last temporary teeth were being replaced by permanent teeth (this pathology was not observed in the above subchronic study, which used dogs that averaged several weeks older at onset of dosing). Four high dose dogs were sacrificed moribund due to persistent and severe oral lesions. Other high dose findings were local inflammatory responses and probable responses to stress (3 dogs with stomach ulcers) and poor overall condition of dogs (prostate and epididymal hypoplasia/atrophy). **Acceptable, with no adverse effects. H. Green and C. Aldous, 6/13/00.

52172-019 164680 Duplicate of 50305-031 158380, above.

ONCOGENICITY, RAT

(See Combined, Rat, above)

ONCOGENICITY, MOUSE

NOTE: Due to uncertainties regarding the nature of the "masses" in 3500 ppm females of study 50305-030 152039, below, a "possible adverse effect" designation will continue for this study type until the data requested in the following 1-liner can be evaluated. Aldous, 6/2/00.

50305-030 152039 Mellert, W., K. Deckardt, K. Küttler, and B. Hildebrand, "Dichlorprop-P - Carcinogenicity study in B6C3F1/CrlBR mice", Department of Toxicology, BASF AG, Ludwigshafen, 6/21/96. Project # 76S0187/91105. Fifty B6C3F1/CrlBR mice per sex per group received Dichlorprop-P (94.51% purity) in the diet at concentrations of 0, 40 (6 and 8 mg/kg/day, M and F), or 400 ppm (59 and 78 mg/kg/day in M and F) for 18 months. Additional high dose groups initially on study [males (2000 ppm) and females (3500 ppm)] were sacrificed on day 259 due to excessive toxicity (severe body weight decrements in both sexes, and 50% mortality of females by day 231). Survival in 2000 ppm males and all other groups was high. NOEL = 40 ppm (reduced body weights (M & F), increased kidney weights (F), chronic nephropathy (primarily F), kidney calcification (primarily F), and fatty pigment in renal tubuli (M).
The 400 ppm middle dose level approximated the MTD for males, but not for females, which showed no body weight changes, nor was the degree of histopathology change indicative of an MTD. A complicating issue was that most 3500 ppm females had clinical signs of "palpable mass in abdomen," which were not examined histopathologically. Regarding the "masses", investigators referred the reader to a subchronic study, rather than presenting histopathology data for high dose females which died prior to the decision to terminate that group (discarding tissues of high dose survivors). Many of these deaths occurred much later than the span of a subchronic study, so that it would not be necessary nor appropriate to use subchronic study results to speculate on the nature of the "masses." Since most of the 3500 ppm females which died on study would likely have been preserved in formalin before the decision was made to terminate the group, histopathology of the preserved abdominal tissues of high dose females should be

submitted to establish whether the "masses" were neoplasia. This reviewer recommends that submission of such data should suffice to upgrade this study to acceptable status. Available data do not suffice to determine "adverse effects" status. (H. Green and C. Aldous, 6/9/00).

51432-002 130706 Protocol for 50305-030 152039, above.

50305-023 116056 Another copy of protocol for 50305-030 152039, above.

50305-012, 13, 14, 15. 34289, 34290, 34291, 34292. "Oncogenicity Study in Mice with 2,4-DP Acid" (CDC Research, 12/14/79). 2.4-DP, purity not stated, was admixed with the feed at doses of 25, 100, or 300 mg/kg and fed to 50 CD-1 mice/sex/group for 83 weeks. UNACCEPTABLE (multiple protocol deficiencies). (J. Christopher, 10/21/85) NOTE: The 1985 CDFA review stated: "Adverse effects: Chronic liver disease and increased liver tumors in males." Hepatocellular tumor incidences in males were 7/90, 3/50, 1/50, and 9/50 in controls through increasing dose groups, respectively. There was a single mid-dose male with a hepatocellular carcinoma. Although the 1985 review claimed a statistically significant increase in hepatocellular adenomas at high dose compared to controls, it is not significant, even using a 1-tailed test. There were several high dose liver non-oncogenicity findings reported in one or both sexes, including bile retention and/or bile granulomas, "hepatocellular anisocytosis," hepatocellular regeneration, and hepatocellular necrosis or degeneration. In addition, "hypertrophic rhinitis" was slightly elevated at 300 mg/kg/day in both sexes. Given the lack of apparent oncogenic response, and the relatively high apparent NOEL for the liver and nasal epithelial responses above, this study does not indicate "adverse effects" according to current classification. Study remains **unacceptable**, with no adverse effects. Since the study is **not upgradeable** and since it has been replaced, there is no worksheet to reflect re-examination of this report. Re-examination by Aldous, 6/2/00.

REPRODUCTION, RAT

51432-009 130824 Hellwig, J., "Reproduction study with 2,4-DP in rats: continuous dietary administration over 2 generations (2 litters in the first and 2 litters in the second generation)," BASF AG, Department of Toxicology, Ludwigshafen, Aug. 7, 1992. Project # 70R0820/89046. Wistar rats, 25/sex/group, were dosed continuously for two generations with racemic Dichlorprop (99.7% a.i.) at 0, 80, 400, or 2000 ppm in diet. There were two mating periods per generation. Systemic toxicity NOEL = 80 ppm, equivalent to 7.8 mg/kg/day, based on slight increase in kidney weights in 400 ppm males. There was also an equivocal increase in degree of findings such as "foci of basophilic tubules" and "papillary/medullary calculi" limited to F0 males at 400 ppm. There were increased incidences or degrees of these kidney changes at 2000 ppm in both sexes and in both generations, suggesting that the small increases at 400 ppm were plausibly treatment effects. Reproductive effects NOEL = 400 ppm (39 mg/kg/day, based on F1 males), based on several major effects, including perinatal deaths of pups (consistently fewer pups delivered per litter, great increases in numbers of stillborn pups, high mortality of pups during postnatal days 0-4), substantially retarded pup weight gains throughout lactation, and increased duration of gestation period (about 0.6 days). Maternal care of neonates was frequently visibly "insufficient", and incidences of "umbilical cord not cut" and "placentae not consumed" were elevated in high dose litters. Physical developmental parameters (pinna unfolding, opening of auditory canal, and eye opening) were consistently delayed at this dose level. Common maternal findings at 2000 ppm included modest food consumption decrements during pre-mating and gestation periods, and sharp decrements during lactation in all mating periods. Body weight changes followed a similar pattern. Water consumption, measured only during pre-mating periods, was consistently elevated at 2000 ppm in both sexes. Modest anemia was indicated by reductions in RBC counts, Hb, and HCT, as well as by slightly elevated urinary urobilinogen in F0 parental rats. Altered liver function or reduced general state were indicated by reductions in serum globulin, triglycerides, and cholesterol in both sexes, as well as by elevations of alkaline phosphatase activity in F0 males and F1 females. Study is **acceptable, with no adverse effects. Aldous, 6/14/00.

52172-022 164684 Duplicate of 51432-009 130824, above.

50305-023 116058 Protocol for 51432-009 130824, above.

50305-018 34305, "Reproduction Study in Rats" doses up to 2000 ppm (Huntingdon Research Center, HRC # 1-361, 10/78). Study is incomplete and **UNACCEPTABLE** (Insufficient information). (J. Christopher, 11/1/85).

TERATOLOGY, RAT

** 52172-021; 164683; "Study of the Prenatal Toxicity of Dichlorprop-P in Rats After Oral Administration (Gavage)" (Hellwig, J., BASF Aktiengesellschaft, Dept. of Toxicology, D-W6700 Ludwigshafen, FRG, Project No. 30R0187/91030, 3/22/93). Twenty five mated female Wistar rats [Chbb: THOM (SPF)] per dose level were administered test article Dichlorprop-P (Batch No. 91-1, $\geq$ 94.5% pure) at 0 (0.5% carboxymethyl cellulose), 20, 80 and 160 mg/kg by oral gavage on days 6-15 post coitum (p.c.). Dams were sacrificed on day 20 p.c., followed by maternal and fetal necropsy. One high dose animal was found dead on day 13. That dam, and a second high dose dam, were the only animals to suffer clinical signs, which included labored respiration (the mortality only) and reduced general state (both animals). Necropsy revealed stomach erosion(s) in both animals, which were considered treatment-induced. Dams administered 160 mg/kg (days 6-15 p.c., $p<0.01$) and 80 mg/kg (days 6-8, 10-13 p.c., $p<0.05$) had lower food consumption compared to controls. Correspondingly, bodyweights were also reduced relative to controls at 160 mg/kg (days 10, 13, 15, 17 p.c., $p<0.05$) and 80 mg/kg (days 13, 15 p.c., $p<0.05$). Reproduction parameters were unaffected. Mean fetal bodyweights of high dose males and females were significantly ($p<0.01$) lower than controls. High dose fetuses also exhibited a higher incidence of rudimentary cervical rib(s) relative to the concurrent controls ($p<0.01$), which was also outside the range of historical controls. This was considered a treatment-related effect of maternal stress rather than a direct teratogenic effect, and references were cited to support this conclusion. The incidences of "sternebra(e) not ossified" and "sternbra(e) incompletely ossified or reduced in size" were elevated in high dose fetuses relative to controls ($p<0.01$), with the former retardation being outside the range of historical controls. Once again, the authors argue that these treatment-related fetal changes were indirect, resulting from decreased fetal size caused by maternal toxicity. In support of this conclusion was the absence of test article effects on fetal malformations. **No adverse effects indicated. Maternal NOEL: 20 mg/kg/day** (based on decreased food consumption and bodyweight gain in dams administered 80 mg/kg/day). **Developmental NOEL: 80 mg/kg/day** (based on increased incidences of variations and retardations, and reduced weight, in fetuses from dams administered 160 mg/kg/day). **Study acceptable** (Vidair 6/6/00).

51432-003 130708 Exact duplicate of 52172-021 164683, above.

50305-023 116057 Protocol for 52172-021 164683, above

50305-017, 019 34303, 34306, 34307. "2,4-DP Oral Teratogenicity Study in the Rat", (Hazelton, Laboratories, UK, January 1980). 2,4-DP, purity not stated, was administered at concentration of 0 (1% methyl cellulose), 8, 20, 50/80 or 125 mg/kg/day to 20 Sprague Dawley pregnant rats/group during gestation days 6 through 15. No maternal or developmental toxicity; complete report; inadequate study (doses too low, too few animals, no analytical chemistry). **Unacceptable and not upgradeable**. (Christopher, 10/31/85).

TERATOLOGY, RABBIT

** 52172-020; 164682; "Study of the Prenatal Toxicity of Dichlorprop-P in Rabbits After Oral Administration (Gavage)" (Hellwig, J., Dept. of Toxicology of BASF Aktiengesellschaft, Ludwigshafen/Rhein, FRG, Project No. 40R0187/91031, 5/19/93). Fifteen artificially inseminated Himalayan rabbits [Chbb:HM(outbred strain)] per dose level were administered test article Dichlorprop-P (Batch no. 91-1, $\geq$ 94.5% pure) at 0 (0.5% carboxymethyl cellulose), 20, 50 and 100 mg/kg by oral gavage on days 7-19 post-insemination (p.i.). Does were sacrificed on day 29 p.i., followed by maternal and fetal necropsy. One high dose animal was sacrificed moribund on day 18 p.i. and one was found dead on day 22 p.i.. A single animal at 50 mg/kg was sacrificed moribund on day 15 p.i., following a spontaneous fracture of the right hindlimb. The two high dose mortalities were considered treatment-related since both animals exhibited "reduced general state" and "no defecation" in the days before death or sacrifice, and both contained severe stomach ulcerations, with one also exhibiting bloody contents of the small intestines. The only other clear maternal effect was significantly reduced food consumption ($p < 0.01$) in high dose dams from days 7-19 p.i.. Reproduction parameters were unaffected. The single developmental change noted in high dose fetuses was that of an increased incidence of accessory 13th ribs ($p < 0.01$). This incidence was above the range for historical controls. The authors argue that this common variation is evidence of maternal stress rather than a developmental defect, and references are cited which support this interpretation. Total fetal skeletal variations and malformations were unaffected. **No adverse effects indicated. Maternal NOEL: 50 mg/kg/day** (based on mortality and reduced food consumption in dams administered 100 mg/kg/day). **Developmental NOEL: 50 mg/kg/day** (based on an increased incidence of accessory 13th ribs in fetuses from does administered 100 mg/kg/day). **Study acceptable** (Vidair 6/2/00).

51432-002 130707 Exact duplicate of 52172-020 164682, above.

51432-001 115741 Protocol for 52172-020 164682, above.

50305-017, 019. 34302, 34308. "2,4-DP Oral Teratogenicity Study in the Dutch Belted Rabbit", (Hazelton Laboratories, UK, September 1979). 2,4-DP purity not given, was administered at concentrations of 0 (1% methyl cellulose), 12, 30, or 75 mg/kg to 15 Dutch Belted pregnant female rabbits/group during gestation days 6-18. Teratogenicity data inconclusive at high dose; report is complete, study is inadequate (no analytical chemistry, doses too low, too few animals/group. **Unacceptable**. **Not upgradeable**. (Christopher, 11/1/85).

GENE MUTATION

** 52172-023; 164685; "Ames *Salmonella Typhimurium* Bacterial Reverse Mutation Assay on 2,4-DP-p Acid" (Jones, E., et al., Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England, Study No. JEL 43/921057, 5/19/93). *S. typhimurium* tester strains TA98, TA100, TA1535 and TA1537 were exposed to 2,4-DP-p Acid (Batch No. 91-1, 95.6% pure) at 0 (methanol) to 5000 ug/plate for 3 days at 37^{o}C, and assayed for reversion to histidine prototrophy. Two independent trials were run using 3 replicate plates per condition, each trial in the presence and absence of S9 microsomal fractions. The test article was not cytotoxic. Furthermore, no increases in reversion frequency were observed in response to the test article. In contrast, positive controls were functional. The results show that the test article is not mutagenic in this assay. **No adverse effects indicated. Study acceptable** (Vidair 6/8/00).

51432-004 130709. Exact duplicate of 52172-023 164685, reviewed by Vidair.

51432-001 115744 Protocol for Record # 130709, above

** 52172-024; 164686; "Chinese Hamster Ovary/HGPRT Locus Assay 2,4-DP-p Acid"

(Adams, K., et al., Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England, Study No. JEL89/931161, 12/9/93). Test article 2,4-DP-p Acid (Batch No. 91-1, 95.6% pure) was evaluated for its induction of mutations at the HGPRT locus in Chinese hamster ovary cells (CHO-K1-BH_4). Concentrations ranging from 0 to 625 ug/ml were tested in the absence of S9 microsomal fractions, and 0 to 850 ug/ml in their presence. Two independent trials were conducted in the absence of S9 and two independent trials in its presence, with duplicate cultures used per condition. Exposure to test article (or negative or positive controls) was for 4 hrs at 37^{o}C, followed by plating of sparse cultures for cytotoxicity determination, and of denser cultures for 7 days of subculture to allow for mutation expression. Then, mutant selection was performed by colony assay in medium containing 6-thioguanine (10 ug/ml). In the absence of activation by S9, levels of test article which reduced colony formation to 65% that of the negative control did cause some increases in the mutant frequency per surviving cell; however, there was no dose-response and the mutant frequencies were within the range of historical controls. Similar results were obtained in the presence of S9, where the test article reduced colony formation to 44% that of the negative control. In contrast, positive controls caused large increases in mutant frequencies that were outside the ranges of historical controls. Thus, it was concluded that the test article is not mutagenic in this assay. **No adverse effects indicated. Study acceptable** (Vidair 6/8/00).

51432-006 130711 Exact duplicate of 52172-024 164686, reviewed by Vidair

** 52172-058; 164720; "Ames *Salmonella Typhimurium* Bacterial Reverse Mutation Assay on 2,4-DP-p 2-EHE" (Jones, E., et al., Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England, Study No. JEL 42/921056, 5/19/93). Test article 2,4-DP-p 2-EHE (Batch No. 5006, 93.2% pure) was evaluated for its ability to induce reversion in the auxotrophic mutant strains of *S. typhimurium*, TA98, TA100, TA1535 and TA1537. Reversion to histidine prototrophy, by concentrations ranging from 0 (ethanol) to 5000 ug/plate, was measured both in the absence and presence of an activating S9 microsomal fraction. Each condition was tested in triplicate plates, and two independent trials were run. Exposure was for 3 days at 37^{o}C. The test article induced no cytotoxicity up to the highest level tested (5000 ug/plate). Furthermore, it did not induce any dose-dependent increases in the number of revertant colonies per plate. In contrast, positive controls were functional. Therefore, it was concluded that the test article is nonmutagenic in this assay. **No adverse effects indicated. Study acceptable** (Vidair 6/15/00).

** 52172-060; 164722; "Chinese Hamster Ovary/HGPRT Locus Assay 2,4-DP-p 2EHE" (Adams, K., Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England, Study No. JEL65/921556, 7/19/93). Test article 2,4-DP-p 2EHE (Batch No. 5006, 93.2% pure) was evaluated for the induction of mutations at the HGPRT locus in Chinese hamster ovary cells (CHO-K1-BH_4). Concentrations up to 250 ug/ml were tested in the absence of an S9 microsomal fraction, and up to 500 ug/ml in the presence of S9. Exposure to test article was for 4 hrs at 37^{o}C, followed by incubation for 7 days (with subculture) to allow for mutation expression. Mutant selection was performed by colony assay in the presence of 6-thioguanine (10 ug/ml). Duplicate cultures were tested per condition (4 per negative control), with two independent trials performed in the absence of S9 and two in the presence of S9. The highest concentrations of test article lowered cell survival to 14% (250 ug/ml) and 42% (500 ug/ml) of the negative control in the absence and presence of S9, respectively. No dose-dependent increase in the mutant frequency per 10^6 surviving cells was observed. In contrast, positive controls were functional. Therefore, the test article was judged nonmutagenic in the assay. **No adverse effects indicated. Study acceptable** (Vidair 6/20/00).

** 52172-093; 164776; "Ames *Salmonella Typhimurium* Bacterial Reverse Mutation Assay on 2,4-DP-p DMAS" (Jones, E., et al., Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England, Study No. JEL 41/921055, 5/19/93). *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 were tested for reversion to histidine prototrophy in response to 2,4-DP-p DMAS (Batch No. 9168/4, 61.58% pure) at concentrations

ranging from 0 (water) to 5000 ug of a.i./plate. Exposure was for 3 days at 37°C, both in the absence and presence of an S9 microsomal fraction. Each condition was tested in triplicate plates, in two independent trials (each trial with and without S9). The test article was not cytotoxic up to 5000 ug/plate. Furthermore, it caused no dose-dependent increases in the mean numbers of revertant colonies per plate. In contrast, positive controls were functional. Therefore, the test article was judged nonmutagenic in the assay. **No adverse effects indicated. Study acceptable** (Vidair 6/21/00).

** 52172-096; 164779; "Chinese Hamster Ovary/HGPRT Locus Assay 2,4-DP-p DMAS" (Adams, K., Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England, Study No. JEL 64/921618, 7/19/93). Test article 2,4-DP-p DMAS (Batch No. 9168/4, 61.58% pure) was evaluated for the induction of mutations at the HGPRT locus in Chinese hamster ovary cells (CHO-K1-BH_4). Concentrations from 0 (water) to 2000 ug/ml were tested in the absence of S9 microsomal fractions, and from 0 to 2500 ug/ml in the presence of S9. Exposure to the test article was for 4 hrs at 37°C, followed by incubation for 7 days (with subculture) to allow for mutation expression. Mutant selection was performed by colony assay in medium containing 6-thioguanine (10 ug/ml). Duplicate cultures were tested per condition, with two independent trials performed in the absence of S9 and two in the presence of S9. The test article lowered cell survival to 23% and 12% of the vehicle-only control in the absence and presence of S9, respectively. No dose-dependent increases in the mutant frequency per 10^6 surviving cells were observed. In contrast, positive controls were functional. The test article was judged nonmutagenic. **No adverse effects indicated. Study acceptable** (Vidair 6/26/00).

** 50305-021 116045, "Report on the Study of 2,4-DP (D-Form) Ames Test", (G. Engelhardt, BASF Aktiengesellschaft, FRG, BASF-Report No. 84/200, 7/31/84). 2.4-DP (D-form), technical grade, 83/22, at concentrations of 0 (DMSO), 20, 100, 500, 2500 and 5000 µg/plate was evaluated for mutagenic potential with *Salmonella typhimurium* strains TA 98, TA00, TA1535, TA1538 and TA1537, 48 hours (37˚C) of exposure. The first and repeat study results indicated no evidence of mutagenicity. ACCEPTABLE. (Kishiyama and Gee, 6/21/2000).

** 50305 - 021 116049, "Mutagenicity Testing - 2,4 Dichlorophenoxypropionic Acid in the Ames Test", (G. Engelhardt, BASF Aktiengesellschaft, Laboratory Project ID 25698n 5M 7107, 22/20441, 3/18/81). 2.4-DP, purity %95%, at concentrations of 0 (DMSO), 20, 100, 500, 2500 and 5000 µg/plate was evaluated for mutagenicity potential to *Salmonella typhimurium* strains TA 98, TA00, TA1535, TA1538 and TA1537, 48 hours (37˚C) exposure, 4 plates per concentration. The trial with TA98 without activation was repeated due to the lack of activity with the positive control in the first trial. No evidence of mutagenicity was reported. ACCEPTABLE. (Kishiyama and Gee, 6/22/2000).

50305-016 34298, "Reverse Mutation Assay: Saccharomyces cerevisiae", (Pharmakon Labs, 1/25/79). 2,4-DP, purity not stated, at concentrations of 0 (DMSO), 0.001, 0.01, 0.10, 1 or 10 mg/ml were evaluated for mutagenicity potential to Saccharomyces cerevisiae. **Adverse effect: Revertant increased at 10 mg/ml.** 59% survival. **UNACCEPTABLE** (No activation and repeat experiment). (J. Remsen 10/22/85).

50305-016 34300, "Reverse Mutation Assay: Saccharomyces cerevisiae", (Pharmakon Labs, 2/6/79). 2,4-DP, purity not stated, at concentrations of 0 (DMSO), 4, 6, 8, 10 or 12 mg/ml were evaluated for mutagenicity potential to Saccharomyces cerevisiae. **Adverse effect: Revertant increased at 6, 8 and 12 mg/ml. UNACCEPTABLE** (No activation and repeat experiment). (J. Remsen 10/22/85).

50305-016 34294, "Ames Salmonella/Microsome Plate test (with and without metabolic activation)", ((Pharmakon Labs, 7/28/78). 2,4-DP, purity not stated, at concentrations of 0.1, 0.5, 2, 8, 40, or 200 mg/plate with and without metabolic activation was evaluated for mutagenicity potential to Salmonella typhimurium strains TA100, TA1538, TA1535, TA1537 and TA98. No evidence of mutagenicity. **UNACCEPTABLE** (no information on test article

composition, no toxicity data). (J. Remsen, 10/23/85).

CHROMOSOME EFFECTS

** 52172-059; 164721; "2,4-DP-p-2-EHE Metaphase Chromosome Analysis of Human Lymphocytes Cultured *In Vitro*" (Akhurst, L., et al., Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England, Study No. JEL 59/921575, 6/28/93). Cultures of normal human lymphocytes, activated for 48 hrs by addition of 175 ug/ml of phytohaemagglutinin, were exposed to 2,4-DP-p-2-EHE (Batch No. 5006, 93.2% pure) at 0 (ethanol) to 80 ug/ml in the absence of activation by S9 microsomal fractions, or 0 to 320 ug/ml in the presence of S9. Cells exposed to the test article in the presence of S9 were resuspended in normal medium after a 3 hr exposure. Mitotic cells were harvested at 13 hrs (10, 20 ug/ml) and 21 hrs (40, 60, 80 ug/ml) after test article addition in the absence of S9, and at 16 hrs (40, 80, 160, 320 ug/ml) after test article addition in the presence of S9. One hundred metaphase cells were scored for structural aberrations per culture. Two replicate cultures were analyzed per test article concentration and per positive control, with four replicates analyzed per negative control. One trial was run. The test article induced some cytotoxicity in the absence of S9, shown by a decreased mitotic index (65% of negative control) in cultures exposed to 80 ug/ml. No cytotoxicity was observed in the presence of S9 up to 320 ug/ml, the concentration at which significant precipitation of test article occurred. In the absence of S9, the test article caused no significant increase in the fraction cells with structural aberrations relative to the negative control. In contrast, the positive control induced a significant increase ($p < 0.001$). In the presence of S9, 320 ug/ml caused a significant increase ($p < 0.05$) in the mean percentage of cells with structural aberrations compared to the negative control (4.5% versus 1.5%). However, since the replicate cultures at this concentration were not in good agreement (1% cells with aberrations versus 8%), and the mean was within the historical control range (0-5.25%), the test article was judged nonmutagenic in the assay. **No adverse effects indicated. Study acceptable** (Vidair 6/19/00).

** 52172-094; 164777; "2,4-DP-p DMAS Metaphase Chromosome Analysis of Human Lymphocytes Cultured *In Vitro*" (Akhurst, L., et al., Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England, Study No. JEL 66/921578, 6/28/93). Normal human lymphocytes, activated for 48 hrs by the addition of phytohaemagglutinin (175 ug/ml), were exposed to 2,4-DP-p DMAS (Batch No. 9168/4, 61.58% pure) at concentrations ranging from 0 (water) to 750 ug/ml in the absence of S9 microsomal fractions, and 0 to 2000 ug/ml in the presence of S9. Exposure was for 13 or 21 hrs in the absence of S9, and 3 hrs in its presence. Mitotic cells were harvested in medium containing colchicine (0.25 ug/ml) at 13 (100 ug/ml) or 21 (500, 750 ug/ml) hrs after addition of test article in the absence of S9, and at 16 hrs (250, 1000, 2000 ug/ml) after its addition in the presence of S9. Duplicate cultures were used for all conditions except solvent-only negative controls, where 4 cultures were used. At least 100 metaphase cells per culture were analyzed for chromosome aberrations, with one trial performed in the presence of S9 and one trial in its absence. In the absence of activation by S9, the test article lowered the mitotic index to 47% that of the negative control, with no significant effect on the fraction of cells containing structural aberrations. In the presence of S9, the highest dose tested (2000 ug/ml) lowered the mitotic index to 57% that of the negative control and caused a highly significant ($p<0.001$) increase in the fraction of cells with structural aberrations (to 11.5%). This level was well outside the range of historical controls (0-5.25%). It was concluded that the test article is clastogenic in the presence of S9 at 2000 ug/ml and above. Positive controls were functional both in the absence and presence of S9. **Possible adverse effect: induction of chromosome aberrations. Study acceptable** (Vidair 6/22/00).

52172-025; 164687; "Chromosome Aberration Assay in Human Lymphocytes *In Vitro* with Dichlorprop-p Acid (Heidemann, A., Cytotest Cell Research GmbH & Co. KG, D-64380 Rossdorf, FRG, Project No. 429300, 2/8/94). Cultures of normal human lymphocytes, activated for 48 hrs by 12 ug/ml of phytohaemagglutinin, were exposed to test article Dichlorprop-p acid (Batch No. N35/172365, 99.3% pure) at concentrations ranging from 0 (ethanol) to 300 ug/ml for 20 or 44 hrs in the absence of an S9 microsomal fraction, or 4 hrs in the presence of S9. At 20 or 44 hrs (300 ug/ml only) after test article addition, mitotic cells were harvested and fixed onto

slides for the scoring of chromosomal aberrations. Duplicate cultures were used per condition, with 100 metaphases scored per culture. Two independent trials were performed in the absence of activation by S9 and two trials in its presence. In the presence of S9, there were no statistically significant ($p<0.05$) increases in the percentages of treated cells with structural aberrations (excluding gaps) relative to solvent-only controls (however, as indicated by the mitotic indices, no cytotoxicity was induced in the presence of S9). In contrast, positive controls were functional. Cultures exposed to the test article at 300 ug/ml in the absence of S9, and harvested at 44 hrs after test article addition, exhibited a significant increase ($0.025>p>0.01$ by the chi-square test) in the percentage of cells with structural aberrations (6.5%) relative to the solvent-only control (1.5%). However, since this increase to 6.5% was only marginally above the range of historical controls (0-3.5%), and the repeat trial did not show a statistically significant increase under identical conditions, it is doubtful that the test article is clastogenic in the absence of S9. **No adverse effects indicated. Study unacceptable due to a failure to use sufficiently high concentrations of test article to induce cytotoxicity in cultures treated in the presence of S9.** (Vidair 6/12/00).

51432-0065 130710 Exact duplicate of 52172-025 164687, reviewed by Vidair

**** 50305 021 116042**, "Mutagenicity Testing - Comparative Cytogenetic Investigations of 2,4-DP Tech. Batches 83 and 85 in Chinese Hamsters - Sister Chromatid Exchange (SCE)", (G. Engelhardt, BASF Aktiengesellschaft, FRG, Laboratory Project I.D. 16M0436/8550, BASF 86/0156, 5/19/86). Dichlorprop technical (2,4-DP), batch 83/48 (purity 93.1%) and batch 85/436 (purity 98.2%) at a concentration of 1780 mg/kg for both batches was evaluated for potential genotoxicity to Chinese Hamster bone marrow cells. Clinical signs included apathy, atony, slight piloerection, irregular respiration and squatting posture. Both batches of dichlorprop slightly increased the number of SCEs/cell relative to the control. The increase was similar for both batches of dichlorprop. UNACCEPTABLE. Not upgradeable (too few dose levels). (Kishiyama and Gee, 6/19/2000).

**** 021 116043**, "Mutagenicity Testing - Cytogenetic Investigations of 2,4-DP in Chinese Hamsters - Bone Marrow Chromosome Analysis", (G. Engelhardt, BASF Aktiengesellschaft, FRG, Laboratory Project I.D. 10M0048/8308, BASF 85/0095, 4/1/85). Dichlorprop technical (2,4-DP; purity 93.1%, batch 83/48) was administered by oral gavage at concentrations of 0 (0.5% CMC), 47, 280 and 1780 mg/kg to 5 Chinese hamsters/sex/group for evaluation of genotoxicity potential to Chinese Hamster bone marrow cells. Death of one high dose female on the second day was reported. Sacrifice times were 6, 24 and 48 hours with all three times investigated at the high dose and only 24 hours at the low and mid doses. Clinical signs were noted at 1780 mg/kg (apathy, atony, piloerection, irregular respiration, squatting posture, trembling and twitching) and to a lesser extent at 280 mg/kg. The author reported no final conclusions can be drawn from the results of the study, based on the aberrations being present in less than 50% of the animals. However, **a possible adverse effect of metaphases with aberrations were increased for the high dose group (1780 mg/kg).** ACCEPTABLE. (Kishiyama and Gee, 6/21/2000).

**** 021 116044**, "Mutagenicity Testing - Cytogenetic Investigations of 2,4-DP in Chinese Hamsters - Sister Chromatid Exchange", (G. Engelhardt, BASF Aktiengesellschaft, FRG, Laboratory Project ID 16M0048/8309, BASF 85/0096, 3/28/85). Dichlorprop technical (2,4-DP); purity 93.1%, batch 83/48, was administered by oral gavage at concentrations of 0 (0.5% CMC), 47, 280 and 1780 mg/kg to 5 Chinese hamsters/sex/group for evaluation (24 hours exposure) of genotoxic potential to Chinese Hamster bone marrow cells (femora). Clinical signs of toxicity (atony and squatting position for the high dose; and apathy, irregular respiration, and piloerection for mid and high dose groups) were observed. SCEs/cell were: 3.31 in controls, 4.67 at 280 me/kg and 7.32 at 1780 mg/kg. **Possible adverse effect: SCE's per metaphase was increased significantly for mid and high dose groups.** ACCEPTABLE (note: the study gives a statement on the study not meeting requirements for 40 CFR 160, GLP). (Kishiyama and Gee,

6/21/2000)

** 50305 - 21 116051, "Report on the Cytogenetic Investigations in Chinese Hamsters after a Single Oral Administration of 2,4-DP; D-Form-Bone Marrow Chromosome Analysis" (G. Engelhardt, BASF Aktiengesellschaft, FRG, RZ-Report No: 85/247, Project No. 10M0215/8414, 8/85). Dichlorprop technical (2,4-DP D form; purity 99 %) was administered by oral gavage at nominal concentrations of 0 (0.5% CMC), 300, 600, or 1200 mg/kg to 5 Chinese hamsters/sex/group for evaluation of mutagenicity potential to Chinese Hamster bone marrow cells. Clinical signs of toxicity (irregular breathing, piloerection and squatting posture) were observed at all 2,4-DP dose levels. Animals in the control and high dose groups were sacrificed at 6, 24 or 48 hours for evaluation. Other groups including positive control were sacrificed at 24 hours. Evaluation of the bone marrow revealed no significant increase in aberrations with 2,4-DP. Analysis indicated that the actual doses of 2,4-DP were 235, 488 or 939 mg/kg. ACCEPTABLE. (Kishiyama and Gee, 6/22/2000).

50305-016 34301, "GNMU Toxicology: Micronucleus Test" (Pharmakon, 2/20/79). 2,4-DP, purity not stated, was administered by oral gavage at concentrations of 0 (water), 25 or 50 mg/kg to 4 CF-1 mice/sex/group, evaluated for mutagenicity potential, 6 hours after the second dose. The number of micronucleated polychromatic erythrocytes did not increase. **UNACCEPTABLE** (single sampling time, too few animals, no evidence of toxicity at the high dose, insufficient information). (J. Remsen, 10/22/85).

50305-016 34293, "Dominant Lethal Assay", (Pharmakon, 3/19/79). 2,4-DP, purity not stated, was administered by oral gavage at concentrations of 0 (0.25% methyl cellulose), 10, 25, or 50 mg/kg to 10 Sprague-Dawley COBS CD male rats/group and evaluated for mutagenicity. No toxic or dominant lethal effects reported. **UNACCEPTABLE** (too few animals). (J. Remsen, 10/23/85).

51432-001 115746 -Protocol for a Mouse micronucleus test (5 May 1992). Probably 52172-095:164778, below.

DNA DAMAGE

** 52172-061; 164723; “2,4-DP-p-2EHE Micronucleus Test (Proudlock, R., Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England, Report No. JEL 45/921200, 5/18/93). Fifteen outbred Swiss CD-1 mice per sex per dose level were administered 2,4-DP-p-2EHE (Batch No. 5006, 93.2% pure) by single-dose oral gavage at 0 (1% methylcellulose), 250, 500 and 1000 (5 extra males and females) mg/kg. Five males and five females were sacrificed at 24, 48 and 72 hrs after dosing, and their femoral bone marrow used to make blood smears on microscope slides. 1000 polychromatic erythrocytes (PCEs) per animal were scored for micronuclei. The normochromatic erythrocytes (NCEs) were also counted in the same fields. A single trial was run. The only clinical signs occurred in high dose animals; slight lethargy and slight pilo-erection, clearing by 45 hrs post-dosing. The test article caused no dose-dependent increases in the mean frequency of micronucleated PCEs, or in the total percentage of micronucleated NCEs. In addition, the ratio of PCE/PCE + NCE was unaffected. In contrast, the positive control substance mitomycin C (12 mg/kg, sacrifice at 24 hrs post-dosing) caused a significant ($p < 0.001$) increase in the mean frequency of micronucleated PCEs. **No adverse effects indicated. Study acceptable** (Vidair 6/20/00).

** 52172-095; 164778; “2,4-DP-p DMAS Mouse Micronucleus Test” (Proudlock, R., et al., Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England, Report No. JEL 44/921199, 5/24/93). Fifteen outbred Swiss CD-1 mice per sex per dose level were administered 2,4-DP-p DMAS (Batch No. 9168/4, 61.58% pure) by single-dose oral gavage at 0 (water), 96, 192 and 384 (5 extra males and females dosed) mg of a.i./kg. Five males and females were sacrificed at 24, 48 and 72 hrs post-dosing, and their femoral bone marrow used to make blood smears on microscope slides. 1000 polychromatic erythrocytes

(PCEs) per animal were scored for micronuclei. Normochromatic erythrocytes (NCEs) in the same fields were also counted. A singe trial was run. Animals administered 192 mg/kg exhibited slight pilo-erection. High dose animals exhibited lethargy, pilo-erection, increased respiration and hunched posture, clearing by 70 hrs. The test article caused no dose-dependent increases in the frequencies of micronucleated PCEs or NCEs relative to vehicle-only controls. In contrast, mitomycin C (12 mg/kg) caused a significant ($p<0.001$) increase in the mean frequency of micronucleated PCEs. High dose animals sacrificed at 48 hrs had a significantly ($p<0.01$) decreased PCE/PCE + NCE ratio relative to the vehicle-only control, suggestive of low level test article-induced bone marrow suppression. **No adverse effects indicated. Study acceptable** (Vidair 6/22/00).

** 50305 - 028 134574, "*In Vivo/In vitro* Unscheduled DNA Synthesis in Rat Hepatocytes with Dichlorprop-p Acid", (R. Fautz, Cytotest Cell Research GmbH & Co. KG, Project No. 429302, BASF 94/11669, 12/20/94). Dichlorprop-p acid, purity 99.3%, administered orally at concentrations of 500 mg/kg (2 hours exposure) and 0 (0.5% CMC), 50, 200 and 500 mg/kg (16 hours exposure) to 5 male Wistar rats/group to determine its potential to induce DNA repair in the rat hepatocytes. Hepatocytes of four animals per group were evaluated by autoradiography, 100 cells per animal. The test article, 2,4DP did not increase the net nuclear grain count. ACCEPTABLE. . (Kishiyama and Gee, 6/22/2000).

50305-016 34299, "Mitotic Gene Conversion, Saccharomyces cerevisiae", (Pharmakon Labs, 2/5/79). 2,4-DP, purity not stated, at concentrations of 4, 6, 8, 10, or 12 mg/ml was evaluated for conversion of Saccharomyces cerevisiae cells. **Adverse effect:** Mitotic gene conversion was increased at 6, 8, and 10 mg/ml levels. **UNACCEPTABLE**. (no metabolic activation was included). (J. Remsen, 10/22/85).

50305-016 34297, "Mitotic Gene Conversion: Saccharomyces cerevisiae" (Pharmakon Labs, 1/5/79). 2,4-DP, purity not stated, at concentrations of 4, 6, 8, 10, or 12 mg/ml with activation only was evaluated for conversion of Saccharomyces cerevisiae cells. **Adverse effect:** Mitotic gene conversion was increased at 10 mg/ml. **UNACCEPTABLE** (No activation was included; no repeat study, no justification for 1 hour treatment, insufficient information). J. Remsen, 10/22/85).

50305-016 34296, "Mitotic Gene Conversion: Saccharomyces cerevisiae" (Pharmakon Labs, 1/25/79). 2,4-DP, purity not stated, at concentrations of 0 (DMSO), .001, .01, .1 1.0, or 10 mg/ml without activation was evaluated for conversion effect on Saccharomyces cerevisiae cells. No evidence of mitotic crossing over. **UNACCEPTABLE** (no use of metabolic activation, test article not described, use of DMSO as a solvent, no repeat test and no justification of 1 hour exposure time). (J. Remsen 10/23/85).

50305-016 34295, "Pharmakon DNA Damage: Escherichia coli Plate Test" ((Pharmakon Labs, 11/20/78). 2,4-DP, purity not stated, at concentrations of 0 (DMSO), .001, .01, .1 1.0, or 10 mg/ml with and without activation was evaluated for DNA damage to Escherichia coli cells. **Adverse effect:** Larger zone of inhibition with repair deficient strain E coli at 800 mg/ml with activation. **UNACCEPTABLE** (lacking are information on test article and cytotoxicity; and a repeat test. (J. Remsen, 10/23/85)

NEUROTOXICITY

52172-013; 164671; "Dichlorprop-P – Acute Oral Neurotoxicity Study in Wistar Rats"; (W. Mellert *et. al.*; Department of Toxicology of BASF Aktiengesellschaft, , D-67056 Ludwigshafen/Rhein, FRG; Project ID. 20S0187/91156; 4/24/95); Ten Wistar (Chbb:THOM (SPF)) rats/sex/group received a single oral gavage dose of 0, 125, 250 or 500 mg/kg of 2,4-Dichlorprop-p Technical (batch no. N 39, purity: 92.4%). Six males and two females died in the 500 mg/kg treatment group within 4 days. Due to the excessive mortality of the males in this group, an additional group of 10 males/group were treated with 0 or 400 mg/kg. Functional

observational battery (FOB) and motor activity evaluations were performed 7 days prior to dosing, 3 to 5 hours post-dose on day 0 and on days 7 and 14. The mean body weights of the males in the 400 and 500 mg/kg treatment groups were less than those of the controls at 7 days ($p<0.05$ or 0.01). In the FOB, home cage observations, both males and females in the 250, 400 and 500 mg/kg groups exhibited an abdominal or a lateral posture, apathy and half-closed eyes on day 0. Signs noted in the open field observations for males in the 250, 400 and/or 500 mg/kg groups or the females in the 500 mg/kg group included piloerection, abdominal posture, hypoactivity or apathy, slight tremors, severe convulsions, impairment of gait and/or spreading of fore/hindlimbs, half-closed eyes, and slight hypothermia. Except for the piloerection exhibited by the 400 and 500 mg/kg males at 7 days, no other clinical signs were evident at 7 days. The sensorimotor test/reflex evaluation revealed a retarded righting response for males in the 250 mg/kg group and higher and females in the 500 mg/kg group. Both sexes in the 500 mg/kg group and the males in the 400 mg/kg group demonstrated a lesser or absent pupillary reflex. The males in the 500 mg/kg group made no effort to grasp an object when it was placed in their line of vision. The number of rearings in a 2 minute interval was reduced on day 0 for both sexes at 250 mg/kg and above ($p<0.05$). The mean forelimb grip strength was lower for both sexes in the 500 mg/kg group ($p<0.01$). The mean hindlimb grip strength was lower for males at 250 mg/kg and above and for the females in the 500 mg/kg group ($p<0.002$). Likewise, landing foot-splay was greater for the males at 250 mg/kg and above and for the females in the 500 mg/kg group ($p<0.01$ or $p<0.002$). Motor activity was diminished for the males in the 400 mg/kg group and the females in the 250 and 500 mg/kg groups ($p<0.01$ or 0.002). In the necropsy examination, the decedents in the 500 mg/kg treatment group exhibited foci in the epithelium of the glandular stomach. In addition, the one male which died in the 400 mg/kg group had an erosion/ulcer in the glandular stomach. Discoloration of the contents in the intestinal tract was noted for these animals. Emphysema was reported in the lungs of 4 males and 2 females of the 500 mg/kg group. No gross lesions were noted for the survivors. Microscopic examination of the nervous tissue did not reveal any treatment-related lesions. **NOEL:** (M/F) 125 mg/kg (based upon the treatment-related effects noted in the FOB and motor activity evaluations for the 250 mg/kg group animals). **Study acceptable.** (Moore, 6/5/00)

52172-016; 164675; "Dichlorprop-P – Subchronic Oral Dietary Toxicity and Neurotoxicity Study in Wistar Rats"; (W. Mellert, *et. al.*; Department of Toxicology of BASF Aktiengesellschaft, , D-67056 Ludwigshafen/Rhein, FRG; Project ID. 50C0187/91158; 7/14/95); Fifteen Wistar (Chbb: THOM (SPF)) rats/sex/group were dosed in the diet with 0, 100, 500, 2000 (males only) or 3000 (females only) ppm of 2,4-Dichlorprop-p Technical (batch no. N 39, purity: 97.6% (based on Diclorprop), optical purity: 92.4%) for 13 weeks ((M): 0, 7, 35, 144 mg/kg/day, (F): 8, 42, 245 mg/kg/day). No mortality resulted from the treatment. No treatment-related signs were noted in the general clinical observations. The mean body weight of the 2000 ppm males was less than that of the controls during the first 8 weeks of the study ($p<0.05$ or 0.01). Mean food consumption for these animals was less than that of the controls for the first 2 weeks of the study ($p<0.05$ or 0.01). The mean body weight and food consumption values for the 3000 ppm females were lower than those of the control throughout the study ($p<0.01$). In contrast, mean water consumption for the 2000 ppm males and the 3000 ppm females was greater than that of the controls throughout the study ($p<0.01$). Only the fore- and hindlimb grip strength parameters were apparently affected in the functional observational battery. The values were less than those of the control, ($p<0.05$, 0.02, or 0.002) for all of the treated females (forelimb) and 100 and 3000 ppm females (hindlimb) only after 22 days of dosing. The mean values for these treated animals were all within the historical control range. Mean motor activity was reduced for the 3000 ppm females at the 50 day time point ($p<0.02$). Otherwise, no other apparent treatment-related effect on activity was noted. For hematology, rbc, hemoglobin, and hematocrit, values were less than those of the controls for both high dose males and females ($p<0.01$). Among the clinical chemistry parameters, mean serum alkaline phosphatase activity was increased for the 2000 ppm males and the 3000 ppm females ($p<0.01$). In addition, mean globulin, triglycerides, and cholesterol values were less than those of the controls for the high dose males and females ($p<0.05$ or 0.01). In the urinalysis results, specific gravity was lower and the presence of erythrocytes and bacteria was greater for the high dose females ($p<0.01$). No

gross lesions were noted in the necropsy examination. Absolute liver ($p<0.01$) and kidney ($p<0.05$) weights were greater for the high dose females. Relative liver and kidney weights were greater for both high dose males and females ($p<0.05$ or 0.01). No lesions were noted in the nervous tissue derived from the animals receiving perfusion fixation. For the other animals, a decrease in fat storage and an increase in incidence and severity of cytoplasmic eosinophilia and granular cytoplasm in the liver was noted for the high dose males and females. Target organ: liver. No adverse effect evident. NOEL: (M/F) 500 ppm ((M) 35 mg/kg/day, (F): 42 mg/kg/day) (based upon the increased water consumption and the treatment-related effects upon certain of the hematology and clinical chemistry parameters and the histological effects upon the liver noted for the 2000 ppm males and the 3000 ppm females); Study acceptable. (Moore, 6/8/00)

SUBCHRONIC STUDIES

Rat

52172-015; 164674; "Study on the Oral Toxicity of the D-form of 2,4-DP in Rats, Administration in the Diet over 3 Months"; (B. Kuhborth *et. al.*; BASF Aktiengesellschaft, Department of Toxicology, D-6700 Ludwigshafen/Rhein, FRG; Project No. 31S0495/8594; 8/6/87): Ten Wistar rats/sex/group were treated in the diet with 0, 100, 500 or 2500 ppm of 2,4-Dichlorprop-p Technical (purity: 98.4% (optical purity: 93.6%)) for 3 months ((M) 0, 7.2, 36.7, 193 mg/kg/day, (F) 0, 8.3, 41.4 and 208 mg/kg/day). The mean body weights for the males and females in the 2500 ppm treatment group were 8.1 ($p<0.05$) and 8.4% less than those of the control, respectively, at the end of the treatment. Water consumption was markedly increased for both sexes in the high dose group. In the hematology evaluation, mean red blood cell count, mean hemoglobin concentration and mean hematocrit were lower than the controls for both the males ($p<0.05$) and the females in the 2500 ppm group. In the clinical chemistry, the 2500 ppm group had higher mean alanine aminotransferase ($p<0.01$, both sexes), alkaline phosphatase ($p<0.01$ (M), $p<0.05$ (F)), urea ($p<0.01$ (M)), creatinine ($p<0.01$ (M), $p<0.05$, (F)) and total bilirubin ($p<0.01$, both sexes) values than those of the control. The mean globulin ($p<0.01$, both sexes), triglyceride ($p<0.01$, M) and cholesterol ($p<0.01$, M) concentrations for this group were lower than those of the control. The mean absolute liver weights for both sexes in the 2500 ppm group were greater than those of the control ($p<0.05$). The mean relative weights for the kidneys of the 500 ($p<0.05$) and 2500 ppm ($p<0.01$) males and the 2500 ppm ($p<0.01$) females were greater than those of the control. Peripheral fatty infiltration of the liver was lacking in the high dose animals. **Target organ: liver. No adverse effect indicated. NOEL:** (M/F) 500 ppm ((M): 36.7 mg/kg/day, (F) 41.4 mg/kg/day) (based upon the effects on hematology and clinical chemistry parameters, increased mean liver weights and lack of peripheral fatty infiltration in the livers of the 2500 ppm treatment group); **Study acceptable.** (Moore, 5/30/00)

50305-024 116059 Duplicate of rat subchronic study, 52172-015 164674, above.

51432-008; 130716; "Report on the Comparative Study of the Toxicity of the Racemate and D-form of 2,4-DP in Rats after 4-Week Administration in the Diet."; (P. Kirsch; BASF Aktiengesellschaft, D-6700 Ludwigshafen, West Germany; Project No. 30S0048/8331; 3/13/85); Ten Wistar rats/sex/group were fed in the diet 0, 100 or 500 ppm of 2,4-DP racemate (test substance no. 83/48, purity: 93.1%) or 100 or 500 ppm of 2,4-DP D-form (test substance no. 83/22, purity: 97.4%) for 4 weeks (2,4-DP racemate: (M) 8.59, 43.1 mg/kg/day, (F) 9.39, 45.8 mg/kg/day, 2,4-DP D-form: (M) 8.83, 42.4 mg/kg/day, (F) 9.01, 45.0 mg/kg/day). No mortality resulted from the treatment. There were no treatment-related clinical signs nor effects upon mean body weight, food consumption, hematology or clinical chemistry. Necropsy and histopathology did not reveal any treatment-related lesions. **NOEL:** (M/F) 500 ppm (2,4-DP racemate: (M) 43.1 mg/kg/day, (F) 45.8 mg/kg/day, 2,4-DP D-form: (M) 42.4 mg/kg/day, (F) 45.0 mg/kg/day) (based upon the lack of treatment-related effects at the highest dose tested). No apparent difference in toxicity between 2,4-DP racemate or 2,4-DP D-form was evident. **Supplemental Study** (non-guideline study). (Moore, 8/17/00)

092; 164775; "Report: Study of the Dermal Toxicity of Dichlorprop-p-DMA Salt in Wistar Rats Application to the Intact Skin (21 Applications)" (Kirsch, P. et al., Department of Toxicology, BASF Aktiengesellschaft, Rhein, Germany, Laboratory Project Identification 37H0463/91130, Sponsor Report # 95/10055, 1/10/95). 822. Dichlorprop-p-DMA salt (Batch number: 9168/4, purity=61.58% w/w as DMA), diluted with deionized water (low and mid-doses), was applied to the clipped skin of 5 Wistar rats per sex per dose at dose levels of 0 (deionized water), 12, 120, or 1000 mg/kg/day for 6 hours per day, 5 days per week over 4 weeks (21 applications) using a semiocclusive dressing. No mortalities occurred. In one male animal at 1000 mg/kg, grade 2 erythema with scaling after the 5th application and grade 1 erythema with scaling after the 6th application were observed at the test site. In two female animals, grade 1 erythema was observed after the 4th application at the test site. No treatment-related clinical signs were observed. No treatment-related body weight, hematological, or serum chemistry effects were observed. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M/F, systemic)=1000 mg/kg/day based on no effects at the highest dose tested (HDT). NOEL (M/F, skin)=120 mg/kg/day based on irritation effects at the highest dose tested (HDT). **Acceptable**. (Corlett, 8/4/00)

Dog

52172-014; 164672; "Report on the Study of the Toxicity of Dichlorprop-P in Beagle Dogs Administration Via the Diet Over 3 Months" (Hellwig, J., Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen/Rhine, Germany, Project No. 31D0187/91091, Reg. Doc. # BASF 94/10863, 9/15/94). 821. Dichlorprop-P (Batch No. 172365-91-1, purity=95.6%) was admixed to the diet at dose levels of 0 (untreated diet), 25, 175, or 525 ppm (0, 0.7, 5.1, or 15.7 mg/kg/day, respectively, for males and 0, 0.8, 5.8, or 18.1 mg/kg/day, for females) and fed to 5 beagle dogs per sex per dose for 3 months. No mortalities occurred. Treatment-related diarrhea was observed in both sexes at 525 ppm. A treatment-related decrease in mean red blood cell level was observed in both sexes at 525 ppm. A treatment-related decrease in mean triglycerides level was observed in females at 525 ppm. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M)=5.1 mg/kg/day (175 ppm) and NOEL (F)=5.8 mg/kg/day (175 ppm) based on clinical signs (diarrhea), decreased mean red blood cell level, and decreased mean triglycerides level (females only). **Unacceptable but possibly upgradeable** with the submission of an expanded and more comprehensive presentation of the test article homogeneity data including sampling protocol used. (Corlett, 6/8/00)

50305-029 139379 Exact duplicate of 52172-014 164672, above.

Mouse

52172-017; 164676; "Subchronic Oral Toxicity Study with Dichlorprop-p Acid in B6C3F1 Mice Administered in the Diet for 3 Months" (Mellert, W., Dept. of Toxicology, BASF Aktiengesellschaft, D-67056 Ludwigshafen/Rhein, FRG, Project No. 35C001/91001, 9/13/93). Ten B6C3F1 mice per sex per dose level were administered test article Dichlorprop-p acid (Batch No. N 35, 95.88% pure) in their feed at 0, 100, 1000 and 2500 ppm for 92-93 consecutive days. Mean daily intake of the test article was 0/20/224/683 mg/kg for males and 0/33/380/1043 mg/kg for females, corresponding to 0/100/1000/2500 ppm. No treated animal died or displayed any clinical signs. Bodyweight gains in high dose males were reduced relative to controls for all weeks ($p<0.01$) and for 5/13 weeks in males fed 1000 ppm ($p<0.05$). Female bodyweights were unaffected. Platelets were elevated in males at 1000 ($p<0.05$) and 2500 ppm ($p<0.01$) and in females at 2500 ppm ($p<0.05$), all relative to controls. Males exhibited a dose-responsive reduction in triglycerides relative to controls, with the reduction in high dose males being statistically significant ($p<0.01$). Females showed a dose-responsive increase in cholesterol relative to controls, with the increases at the two highest dose levels being statistically significant ($p<0.01$). Two liver enzymatic activities were elevated in high dose animals relative to controls: alkaline phosphatase in serum ($p<0.01$) and cyanide-insensitive palmitoyl-CoA-oxidation (PAL COA) in liver homogenates ($p<0.0001$, tested in controls and high dose animals only). Both absolute ($p<0.01$) and relative ($p<0.01$) liver weights were elevated in high dose males and

females relative to controls. Gross pathology identified discolored liver in both sexes at incidences of 0/0/1/10 for 0/100/1000/2500 ppm. The discoloration and increased weight were probably related to the increased eosinophilic staining of the cytoplasm of hepatocytes, noted in both males and females at incidences of 0/0/0/10. Increased eosinophilic staining of the cytoplasm was also observed in tubular epithelial cells of the kidney in both high dose males (0/0/0/8) and females (0/0/0/10). The incidences of diffuse fatty infiltration of the liver were reduced in both treated males (10/10/2/0) and treated females (5/8/4/0). These microscopic findings were ascribed to peroxisome proliferation, which in previous studies has been associated with increased eosinophilic staining of cellular cytoplasm. Peroxisome proliferation may also be the basis for the reduced fatty infiltration of the liver (increased lipid metabolism) and alterations in alkaline phosphatase, PAL COA, triglycerides and cholesterol. No adverse effects indicated. NOEL (M) = 100 ppm (20 mg/kg/day based on reduced bodyweight gain, increased platelets, and decreased diffuse fatty infiltration of the liver in males fed 1000 ppm); (F) = 100 ppm (33 mg/kg/day based on increased serum cholesterol in females fed 1000 ppm). Study unacceptable due to lack of ophthalmology (Vidair 6/7/00).

51432-007 130712 Duplicate of 52172-017 164676, above.

Rabbit

52172-018; 164678; "Twenty-One Day Dermal Toxicity Study in the Rabbit with 2,4-DP-p Acid"; (S.A. Allan *et. al.*; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. JEL 40/921532; 6/22/93); Five New Zealand White rabbits/sex/group were treated dermally with 0, 10, 100 or 1000 mg/kg/day of 2,4-Dichlorprop-p Technical (acid) (batch no. 91-1, purity: 95.6%) for 6 hours/day, 21 (males) or 22 days (females). No mortality nor signs of toxicity resulted from the treatment. There were no treatment-related effects upon mean body weight or food consumption. Dermal irritation was evident in a dose-related manner with slight to well-defined erythema and edema being noted at the site of application for the 1000 mg/kg/day treatment group. Evaluation of the hematology and clinical chemistry parameters did not reveal any treatment-related effects. The mean urinary protein concentration was increased for the 1000 mg/kg/day males ($p<0.05$). However, no apparent treatment-related lesions were evident in the kidneys of this group. In the necropsy examination, although the mean thyroid ($p<0.05$, for the high dose groups), spleen and testes weights were lower in a dose-related manner, microscopic evaluation of these organs did not reveal any treatment-related effects. Diffuse acanthosis, minimal or moderate in severity, and diffuse inflammatory cells in the superficial dermis, minimal, were evident in the treated skin in a dose-related manner. **No adverse effect indicated. Systemic Toxicity (M/F):** 1000 mg/kg/day (based upon the lack of treatment-related effects on the 1000 mg/kg/day treatment group), **Dermal NOEL (M/F):** < 10 mg/kg/day (based upon abnormal histology of treated skin); **Study acceptable.** (Moore, 6/12/00)

METABOLISM STUDIES

52172-026; 164688; "(^{14}C)-Dichlorprop-P: Absorption, Distribution, Metabolism, and Excretion in the Rat"; (G. Lappin**;** Corning Hazleton (Europe), Harrogate, North Yorkshire, HG3 1PY, England; Study No. 1149/17; 11/26/96); Male and female Wistar Crl:(WI)BR rats were dosed by oral gavage with (^{14}C)-Dichlorprop-P (radiochemical purity: 99.3%, chemical purity: 88.3%, specific activity: 60.224 μCi/mg, radiolabel on the aromatic ring). For Groups A and D, 5 animals/sex were dosed with 5 mg/kg of the test material. In Group B, 5 animals/sex were dosed with 5 mg/kg of unlabeled Dichlorprop-P (batch no. 39/171-2, purity: 99.6%) for 14 days, followed by a single dose of 5 mg/kg of the labeled test material. For Groups C and E, 5 animals/sex were treated with 100 mg/kg of the labeled test material. In Group F, 12 animals/sex were dosed with 5 mg/kg of the labeled material. For Groups A, B and C, urine was collected at 6, 12, 24, 48, 72, 96, 120, 144 and 168 hours after dosing with the radiolabeled material. Feces were collected from these animals at 24, 48, 72, 96, 120, 144 and 168 hours after dosing.

Expired air was collected at 12, 24, 48, 72, 96, 120 and 168 hours after dosing from 2 animals in Group C. Each time excreta were collected, cages were rinsed and the rinsate was analyzed for radioactivity. Analysis of the radiolabel in various tissues and organs was performed at the end of 7 days. For Groups D and E, blood was collected from the caudal vein at 0 (pre-dose), 1.5, 3, 6, 9, 12, 24, 48, 72, 120 and 168 hours after dosing. For Group F, 4 animals/sex were euthanized at 1, 3, and 6 hours after dosing and tissues and organs analyzed for the presence of radiolabeled material. Excretion of the administered dose occurred largely in the urine during the first 24 hours after dosing. For both sexes, 94.3% or greater of the radiolabel was recovered for Groups A and B by 24 hours and 62.2% or greater was recovered in the urine. Another 11.5% or greater was recovered in the cage wash. For the females in Group C, excretion of the radiolabel was similar with 91.5% of the administered dose excreted in the first 24 hours (65.2% in the urine, 6.6% in the feces and 19.8% recovered in the cage wash). In contrast, for the males in Group C, excretion was less rapid with 61% of the radiolabel recovered in the first 24 hours. By 48 hours, 95.6% of the dose was excreted with 77.5% in the urine, 11.0% in the feces and 7.0% in the cage wash. Metabolism of the test material was minimal. Recovery of metabolites was largely limited to the urine with measurable quantities isolated in the first 6 hours after dosing. The parent compound represented 70% or greater of the recovered radiolabel for the males and 88.8% or greater for the females for these samples. Treatment with β-glucuronidase or sulphatase or with HCL or NaOH did not alter the profile appreciably. The test material was largely absorbed as indicated by the high percentage excreted in the urine. Maximal plasma concentrations were achieved at 2 to 3 hours after dosing (5 mg/kg) or 4 to 5.5 hours after dosing (100 mg/kg). The mean T1/2 values for elimination ranged from 4.4 to 16.5 hours. The wide range in the elimination half-life resulted from the variability in values contributed by a few of the animals. When these outliers were not included in the calculation, the mean T1/2 values ranged from 4.4 to 7.3 hours. Maximal tissue concentrations were noted at 1 or 3 hours after dosing with the higher concentrations of the radiolabel in the heart, lung, liver, kidneys, thyroid and adrenals. **Study acceptable.** (Moore, 6/19/00)

52172-097; 164780; "(^{14}C)-Dichlorprop-p DMA Salt [(^{14}C)-Dichlorprop-p-dimethyl-ammonium]: Metabolism/degradation in Plasma, Gastro-intestinal Tract, Gastro-Intestinal Tract Contents and Post-Mitochondrial Liver Fraction (S9)"; (S.A. John and J.C. Noctor; Corning Hazleton (Europe), Harrogate, North Yorkshire, HG3 1PY, England; Study No. 1149/13; 6/22/95); *In vitro* incubations of plasma (Test System I), stomach contents (Test System II), gastrointestinal tract tissue (jejunum) (Test System III), and liver S9 fraction (Test System IV), derived from male Wistar rats, were performed with (^{14}C)-Dichlorprop-P-DMA ((^{14}C)-Dichlorprop-P-acid, batch no. 476-02, radiochemical purity: 99.0%, specific activity: 6.05 mBq/mg, chemical purity: 99.3%, radiolabel on the aromatic ring and DMA solution, batch no. DG/4/30, purity: 55.3%) for 30 minutes at 37^{o} C. The concentrations of the test material in the respective incubations were as follows: (I) 8.59 mg/ml, (II) 410.1 mg/ml, (III) 118.2 mg/ml, and (IV) 8.59 mg/ml. The incubations of Test Systems I, II, and IV included the test material in the presence of plasma, stomach contents or liver S9 fraction. In Test System III, a section of the jejunum was everted with the serosal surface being on the inside and the mucosal lining on the outside. The ends of jejunum were sewn closed. The tissue was placed in a beaker filled with the test material in a buffer solution. Dichlorprop-P was the only moiety recovered in any of the incubations (96.91% or greater of the radiolabel in the incubation). As the test material was in a salt mixture, a high percentage of recovery would be expected. No apparent metabolism of the acid moiety occurred in any of the incubations. **Study supplemental**. (Moore, 6/22/00)

52172-062; 164724; "(^{14}C)-2-Ethylhexyl Dichlorprop-P: Metabolism/degradation in Plasma, Gastro-intestinal Tract, Gastro-Intestinal Tract Contents and Post-Mitochondrial Liver Fraction (S9)"; (John, S.A.; Corning Hazleton (Europe), Harrogate, North Yorkshire, HG3 1PY, England; Study No. 1149/12; 5/23/96); *In vitro* incubations of plasma (Test System I), stomach contents (Test System II), gastrointestinal tract tissue (jejunum) (Test System III), and liver S9 fraction (Test System IV), derived from male Wistar rats, were performed with (^{14}C)-2-Ethylhexyl Dichlorprop-P (batch no. 432-17, radiochemical purity: 99.3%, specific activity: 39.7 μCi/mg, radiolabel on the aromatic ring) for 30 minutes at 37^{o} C. The concentrations of the test material

in the respective incubations were as follows: (I) 7.99 mg/ml, (II) 406.3 mg/ml, (III) 122.7 mg/ml, and (IV) 7.99 mg/ml. The incubations of Test Systems I, II, and IV included the test material in the presence of plasma, stomach contents or liver S9 fraction. In Test System III, a section of the jejunum was everted with the serosal surface being on the inside and the mucosal lining on the outside. The ends of jejunum were sewn closed. The tissue was placed in a beaker filled with the test material in a buffer solution. The mucosal environment represented a large portion of the incubation milieu. The predominate reaction was the hydrolysis of the ester linkage between the propionic acid and the ethylhexane which resulted in the formation of Dichlorprop-P. Hydrolysis of the test material was noted in the plasma and liver S9 samples. For the liver S9 fractions, the hydrolysis was apparently greater in the absence of the cofactor, NADPH. Interpretation of the results of Test System III with the jejunum sample was more difficult. The quantity of radiolabel recovered from the serosal fluid was quite low (0.118% of the total radioactivity in the incubation). Sixty six percent of this radioactivity was Dichlorprop-P (0.08% of the total radioactivity in the incubation). In contrast, only 14.81% of the radiolabel in the mucosal fluid was Dichlorprop-P, but represented 14.8% of the total radioactivity in the incubation. Penetration of the test material to the serosal layer was not readily accomplished. Significant hydrolysis of the test material on the mucosal surface apparently occurred without this penetration. The application of these results to an understanding of the *in vivo* pharmacokinetics for 2-Ethylhexyl Dichlorprop-P are questionable. **Study supplemental**. (Moore, 6/20/00)

52172-063; 164725; "(^{14}C)-2,4-DP-P-EHE and (^{14}C)-2,4-DP-P-DMA: Absorption, Distribution, Metabolism and Excretion in the Rat"; (G. Lappin, **:** Corning Hazleton (Europe), Harrogate, North Yorkshire, HG3 1PY, England; Study No. 1149/15; 12/2/96); Five male Wistar Crl: (WI)BR rats/group were dosed orally by gavage with 5 mg/kg of (^{14}C)-Dichlorprop-P-EHE (batch no. 432-17, radiochemical purity: 99.3%, specific activity: 39.7 μCi/mg, chemical purity: 96.4%) or (^{14}C)-Dichlorprop-P-DMA ((^{14}C)-Dichlorprop-P-acid, batch no. 476-02, radiochemical purity: 99.0%, specific activity: 163.6 μCi/mg, chemical purity: 99.3% and DMA solution, batch no. DG4/30, purity: 55.3%). For Groups A and B, blood was collected from the caudal vein at 0 (pre-dose), 0.5, 2, 3, 6, 9, 12, 24, 48, 72, 120 and 168 hours after dosing. For Groups C and D, urine was collected at 6, 12, 24, 48, 72, 96, 120, 144 and 168 hours after dosing. Feces were collected from these animals at 24, 48, 72, 96, 120, 144 and 168 hours post-dose. Expired air was collected at 12, 24, 48, 72, and 96 hours after dosing. Dichlorprop-P-DMA was more rapidly absorbed and recovered in the plasma than (^{14}C)-Dichlorprop-P-EHE (T_{max}: 1.2 hours vs. 3.0 hours) and the C_{max} was greater (23.94 vs. 16.48 μg equiv./g). The $T_{1/2\ Elim}$ was longer for Dichlorprop-P-DMA than Dichlorprop-P-EHE (7.4 hours vs. 3.9 hours). The radioactivity was largely recovered in the urine during the first 24 hours post-dose for both of the test materials (Dichlorprop-P-EHE: 73.3, 4.7 and 9.8% of the total recovered radioactivity for urine, feces and cage wash, respectively, after 24 hours and Dichlorprop-P-DMA: 84.7, 3.6 and 5.0% for urine, feces and cage wash, respectively, after 24 hours). Although a number of unidentified metabolites were isolated by HPLC or TLC, the predominant radiolabeled compound was Dichlorprop-P. Treatment of the pooled urine samples with β-glucuronidase or sulphatase or with HCl or NaOH did not alter the profile of the isolated metabolites. **Study supplemental** (not a guideline study). (Moore, 6/21/00)

50305-022 116052, Reuzel, P. G. J. *et al*. "Sub-Chronic (13-Week) Oral Toxicity Study with 2, 4-Dichloro-Phenoxy Propionic Acid in Beagle Dogs", Centraal Instituut Voor Voedingsonderzoek (Central Institute for Nutrition and Food Research), Utrechtseweg 48, Zeist, The Netherlands, Report # R 6246, May 1980. 4 Beagle dogs per sex per group received diets containing 2,4-Dichlorprop (racemic) (93.3% purity) at 0, 78, 303, and 1210 ppm (0, 3, 12, and 48 mg/kg/day) for 13 weeks. At 1210 ppm (48 mg/kg/day), all 4 males and 3 females were sacrificed *in extremis.* Findings in high dose dogs included severe necrotic lesions in the skin, anorexia, hemorrhagic diarrhea, severe emaciation, polyuria, polydypsia, and reduced bodyweights and food intake. Primary hematologic parameters were depressed. White blood cell counts were elevated. Blood urea nitrogen, bilirubin, and GPT were increased. Total protein, albumin, and α1-globulin were decreased in blood. Urinary specific gravity was low,

and bilirubin was detected in the urine. Fecal blood content was increased. Necropsy signs included skin lesions, and ulcers, and hemorrhages of the gastrointestinal tract. Histopathology found centrilobular degeneration in the liver. Increased blood bilirubin was noted at 303 ppm, and phenol red clearance was reduced at this dose level, indicating impaired kidney function. Apparent NOEL = 78 ppm, or about 3 mg/kg/day. This study was noted in review of a much more recent chronic dog study (50305-031 158380). Because a more recent subchronic dog study was performed using Dichlorprop-P (52172-014 164672), there is no need to create a worksheet on this study, which employed racemic dichlorprop. Aldous, 6/9/00.

Subacute Studies:

50305-025 116064 Kirsch, P., "Report on the comparative study of the toxicity of the racemate and D-form of 2,4-DP in rats after four week administration in the diet", BASF AG, Ludwigshafen. April, 1986. BASF Document No. 86/0088. Ten Wistar rats/sex/group were dosed with either control diet, or 2,4-DP (racemic, 93.1% purity, at 100 or 500 ppm), or Dichlorprop-P (97.4% purity, enriched in the D-isomer, at 100 or 500 ppm) for 4 weeks in a supplemental study. Investigators examined hematology, clinical chemistry, clinical signs, food consumption and body weight effects. At termination, rats were necropsied, and limited histopathology was performed (liver, kidneys, spleen, heart, adrenals, and gross lesions). There were no definitive treatment effects, hence apparent NOEL's for findings evaluated were 500 ppm for both test articles. Although this study had some noted deficiencies and does not address specific data requirements, there is no need for a replacement study. Aldous, 6/6/00.

51432-008 130716 Exact duplicate of 50305-025 116064, above. Spreadsheet and library index list this as record 130717. Number 130716 is in stamp mark on title page.